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A stereoselective total synthesis of (±)-tormesol☆

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This contribution is dedicated in recognition of the seminal contributions to organic synthesis, as well as the insightful training and tutelage of a great many chemistry professionals, to Professor Gilbert Stork (Columbia University) on the occasion of his 90th birthday

Keywords:
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ABSTRACT

A general strategy for the synthesis of both *trans*/*syn*- and *trans*/*anti*-sphenolobane diterpenes has been developed, which utilizes an intramolecular ester enolate alkylation (IEEA) as a key step. A stereoselective total synthesis of (±)-tormesol (**1**), an unusual *trans*/*syn*-sphenolobane diterpene, was accomplished in 18 steps in 4.1% overall yield from readily available aldehyde **16**.

1. Introduction

The sphenolobane (tormesane) diterpenes, have been isolated from phytochemical[2] and marine[3] sources (Fig. 1), and some have very interesting biological activity. They possess a *trans*-fused hydroazulenoid skeleton as a common structural motif, but differ in configuration at C(9).[4] Owing to their interesting molecular structure and potentially useful biological properties,[2a] the sphenolobane diterpenes have received a significant attention from synthetic community, leading to total syntheses[5–7] of several members of this family along with approaches to their synthesis.

The novel diterpene alcohol (+)-tormesol was isolated in 1989 from *Halimium viscosum* collected in the western Iberian Peninsula by Urones and co-workers,[8] whose structural assignment was accomplished through chemical transformations and extensive spectroscopic studies.[9] The tormesol diterpene is an 'extended' daucane skeleton[10] with an eight-carbon side chain appended onto the cyclopentane ring, and it features a challenging *trans*-fused

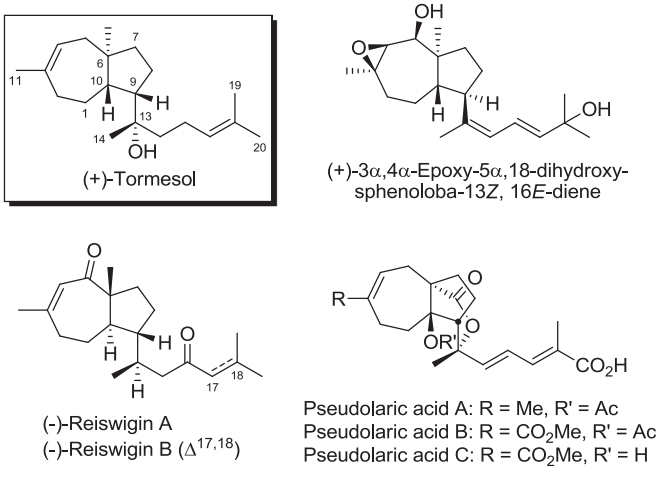

Fig. 1. Representative naturally occurring sphenolobane diterpenoids.

☆ See Ref. 1.

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hydroazulene ring system with four contiguous stereogenic centers on and adjacent to the cyclopentane subunit.

Unlike other sphenolobane diterpenoids, tormesol and pseudolaric acids feature a unique stereochemical relationship: 'trans' between the C(6) CH_3 and the C(10) H and '*syn*' between C(10) H and C(9) H (referred to as trans/*syn* hereafter) at the ring junction and its adjacent site (Fig. 2). This substitution pattern imposes congestion about cyclopentane subunit in that the angular methyl group at C(6) and side chain appended at C(9) project into the same space. This trans/*syn*-configuration of the substituents is thus thermodynamically less stable than that of trans/*anti*-isomer due to the greater amount of conformational steric compression, that is, present.

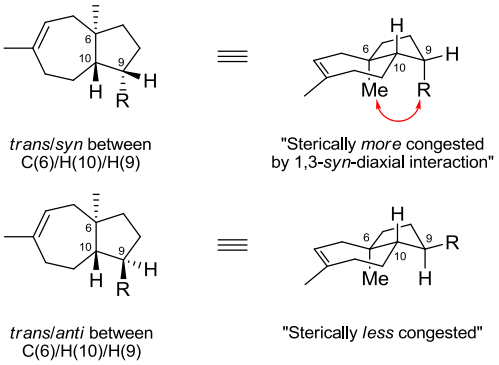


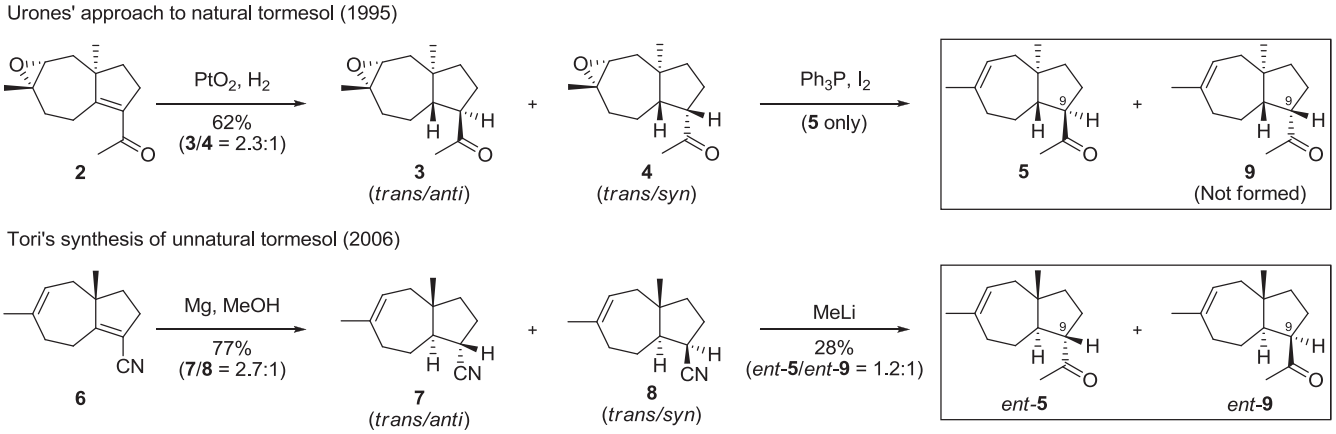
Fig. 2. Conformational analysis of sphenolobane frameworks.

In fact, previous approaches to the installation of this trans/*syn*-configuration encountered difficulties in the creation of C(9) configuration due to facile epimerization (Scheme 1). The required trans/*syn*-configuration across C(6)–C(10)–C(9) can be successfully introduced from readily available conjugated systems **2** and **6**, as even when target intermediates **4** and **8** are obtained, epimerization will inevitably degrade or destroy the hard-won selectivity.

This propensity for epimerization at C(9) is consistent with the analysis of the trans/*anti*-isomer being thermodynamically more stable. Along with these experimental results, molecular mechanics calculations[9b] support the view that trans/*syn*-isomer is less stable (total energy=17.20 kcal/mol) compared with the trans/*anti*-isomer (total energy=13.80 kcal/mol), which explains the difficulty in obtaining the desired trans/*syn*-isomer **9** and preference for forming **5**. Accordingly, the key structural features of this interesting *trans*/*syn*-fused hydroazulenoid diterpene that must be addressed in a total synthesis include: (1) the axially oriented bulky side chain at C(9) that will experience an unfavorable 1,3-*syn*-diaxial interaction with the angular methyl group at C(6) as depicted in Fig. 2 and (2) the *tert*-carbinol moiety at C(13) in the flexible acyclic side chain.

The construction of new carbon–carbon bonds serves a central role in organic synthesis, and the reaction of carbon nucleophiles with carbon electrophiles is an effective means to achieve this purpose. The pioneering efforts of the Stork group have demonstrated that an intramolecular ester enolate alkylation can generate a new carbon–carbon bond in an efficient and stereocontrolled fashion, through which the total syntheses of architecturally complex natural products have been achieved.[11]

Much of our synthetic program over the years has been focused on the development of intramolecular enolate alkylation as a general synthetic methodology for the stereoselective construction of highly functionalized cycloalkanecarboxylates, with particular emphasis on the construction of quaternary carbon centers.[12,13] As a part of this effort, we have developed a general synthetic strategy for these construction of the functionalized cyclopentanecarboxylates (Fig. 3),[14] which constitute an important target structural moiety, that is, frequently encountered in natural product synthesis. Through judicious retrosynthetic disconnections



Scheme 1. Synthetic efforts to install the trans/*syn*-configuration between C(6)/C(10)/C(9) by Urones and Tori.

reported independently by Urones[9b] and Tori.[7a,b] Urones employed hydrogenation with enone **2** to achieve this, although the desired *trans*/*syn* **4** is the minor isomer thus obtained (2.3:1). Tori utilized a dissolving metal reduction on unsaturated nitrile **6**, but the desired trans/*syn* stereochemistry is still disfavored, as the product **8** is the minor isomer (2.7:1). Epimerization at C(9) understandably occurred under both acidic and basic conditions, with **4** having led to only the trans/*anti*-fused isomer **5**, while **8** gave a mixture of trans/*syn*-isomer *ent*-**9** and trans/*anti*-isomer *ent*-**5** as a 1:1 mixture at C(9) in very low yield. This indicates the need for a different strategy to lock in the desired stereochemical relationships, since and the choice of appropriate cyclization precursors, we envisioned that both *trans*/*anti*- and *trans*/*syn*-1,2,3-trisubstituted cyclopentanecarboxylate system could be constructed in a highly stereoselective manner by utilizing our intramolecular ester enolate alkylation (IEEA) strategy. We have employed the Type I disconnection (see Fig. 3 below) in our synthesis of reiswigin A, while the Type II disconnection was exploited in our total synthesis of (±)-tormesol (**1**). These application serve to demonstrate the general feasibility of our IEEA strategy for the stereoselective construction of either a *trans*/*syn*- or *trans*/*anti*-1,2,3-trisubstituted cyclopentane subunit.

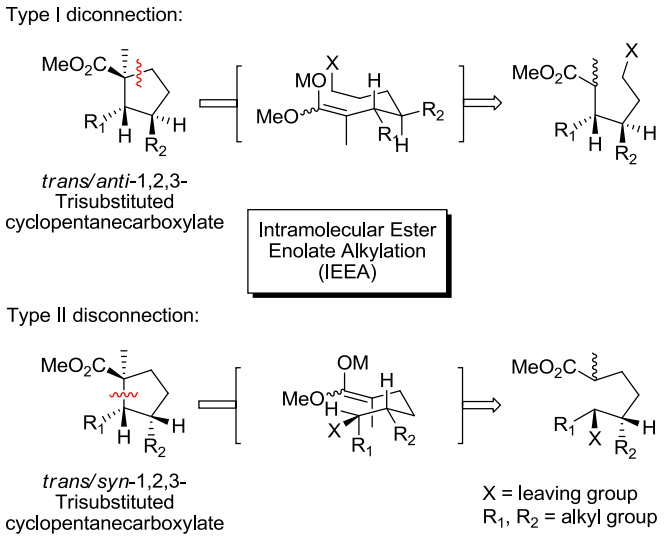


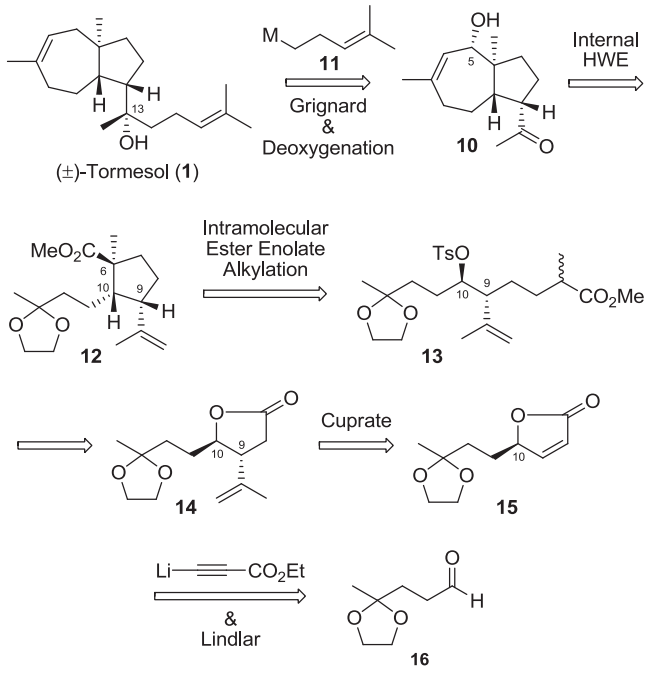
Fig. 3. General Strategy for the 1,2,3-trisubstituted cyclopentanecarboxylates via IEEA strategy.

Herein we wish to report the stereocontrolled total synthesis of (±)-tormesol (**1**), in which our strategy utilizes a '*folding and allylic strain-controlled*' intramolecular ester enolate alkylation (IEEA) and several substrate-controlled diastereoselective reactions as key tactics in the synthesis of this unusual natural product.

2. Results and discussion

2.1. Retrosynthetic analysis and strategy

The strategy envisioned for the synthesis of (±)-tormesol (**1**) is outlined in retrosynthetic form in Scheme 2. We determined that our total synthesis of **1** must address three main synthetic challenges: (1) the implementation of the IEEA tactic for the stereoselective installation of the *trans*/*syn*-fused hydroazulene core with the desired three contiguous stereocenters at C(6), C(10), and C(9); (2) the feasibility of constructing the medium-sized cycloheptene subunit of the target structure through an intramolecular Horner–Wadsworth–Emmons olefination; and (3) the substrate-controlled diastereoselective reaction for the assembly of the side chain at C(13).



Scheme 2. Retrosynthetic plan for (±)-tormesol (**1**).

With these goals in mind, we identified *trans*-fused bicyclic ketone **10** as a reasonable late-stage precursor to the target molecule (Scheme 2). The potential instability of the *tert*-carbinol functionality at C(13) argued for its incorporation late in the sequence, and the side chain was installed through coupling between bicyclic ketone **10** and homoprenyl nucleophile **11** in a stereoselective manner via substrate-controlled diastereoselective reaction. In this scenario, we anticipated that nucleophilic attack at the ketone carbonyl would occur most readily from the less hindered *si*-face on the conformer depicted in Fig. 4. Such an approach would involve a conformation that minimizes the steric interactions between the angular methyl group at C(6) and the methyl ketone at C(9). Such an analysis is supported by DFT calculations, which show the conformation in which the carbonyl oxygen is oriented toward C(6) is favored by 2.1 kcal/mol (at both the B3LYP and M06-2X levels of theory) over the sterically more congested conformation. Additionally, this advanced-stage assembly strategy lessens the risk in carrying this potentially unstable *tert*-carbinol functionality through any additional synthetic steps required for the construction of this molecule.

Continuing with our analysis and as mentioned above, the bicyclic framework of **10** might arise from key intermediate **12** by means of an intramolecular Horner–Wadsworth–Emmons (HWE) reaction (Scheme 2). We anticipated that **12**, which embodies the desired relative stereochemistry, would be most efficiently crafted through the '*folding and allylic strain-controlled*' IEEA developed by our laboratory. This would enable the creation of a new quaternary center in a densely substituted environment, one of the central issues to be resolved in this synthetic endeavor. We postulated that an *anti*-arrangement between a leaving group at C(10) and its vicinal alkyl substituent at C(9) in **13** would be suitable for our purpose in that this set-up ensures the cis-arrangement between C(10) and C(9) resulting from a specific '*H-eclipsed*' transition state geometry during the cyclization process (vide infra).[13] For this crucial operation, we anticipated that key cyclization precursor **13** could be obtained under effective steric control by employing the butenolide building block **15**, which is readily available from known aldehyde **16**.

2.2. Preparation of key cyclization precursor 13

Our synthesis commenced with preparation of butenolide **15** (Scheme 3). Addition of the acetylide anion derived from ethyl propionate to the known aldehyde **16**[15] in THF at −78 °C afforded propargyl alcohol **17** in 81% yield. Partial reduction of the resulting acetylenic ester **17** with the Lindlar catalyst in EtOAc/pyridine (10:1) following Overman's protocol[16] furnished the desired butenolide **15** in 83% yield.

We selected an isopropenyl group for the required introduction, trans to the appendage at C(10), of a substituent destined to become the ketone residue of bicyclic core **10** (Scheme 3). Stereospecific conjugate addition of isopropenyl Grignard to the butenolide **15** in the presence of CuI in Et_2O at −50 °C afforded the desired *trans*-disubstituted lactone **14** as a single diastereomer in 76% yield. Elaboration of **14** toward our key cyclization precursor **13** required the introduction of the ester moiety and a leaving group for the internal alkylation. This goal was achieved through the reduction of lactone **14** with DIBAL-H to the corresponding lactol **18**, which underwent Wittig olefination with (carbomethoxyethylidene)triphenylphosphorane to furnish α,β-unsaturated ester

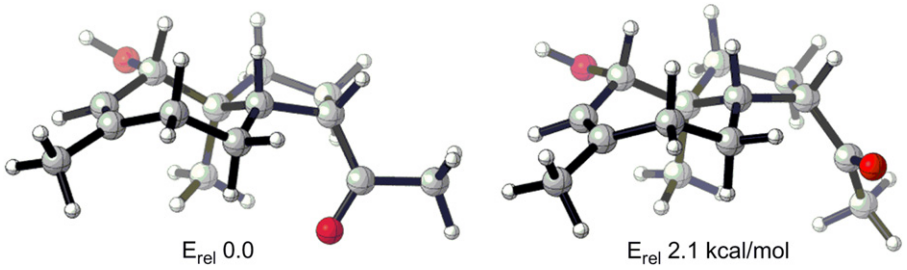
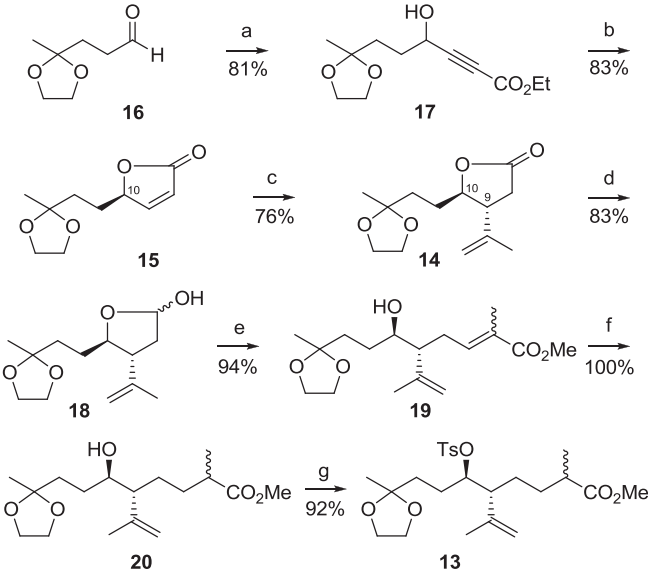
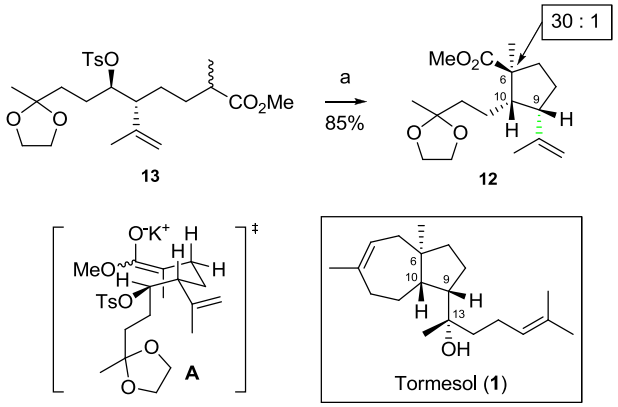


Fig. 4. Conformational analysis of bicyclic ketone **10**.



Scheme 3. Reagents and conditions: (a) $HCCCO_2Et$, *n*-BuLi, THF, −78 °C, 1 h (81%); (b) Lindlar catalyst, H_2, EtOAc/pyridine (10:1), rt, 4 h (83%); (c) isopropenylmagnesium bromide, CuI, Et_2O, −55 °C, 10 min (76%, *de*=100%); (d) DIBAL-H, toluene, −78 °C, 0.5 h (83%); (e) $Ph_3P{=}C(Me)CO_2Me$, CH_2Cl_2, rt, 24 h (*E*/*Z*=95:5, 94%); (f) Mg (50 mesh), MeOH, rt, 12 h (100%); (g) TsCl, pyridine, rt, 24 h (92%).



Scheme 4. Reagents and conditions: KHMDS (4 equiv), THF (0.01 M), −60 °C to 0 °C, 1 h (30:1 at C(6), 85%).

19 in good yield (78% over two steps), exhibiting high stereoselectivity (*E*/*Z*=95:5), that is, nonetheless to be rendered inconsequential. Chemoselective reduction of the conjugated double bond in hydroxyester **19** with Mg in dry MeOH[17] provided ester **20**, and finally tosylation of the resulting **20** afforded the key cyclization precursor **13** in excellent yield (92% over two steps).

2.3. Key cyclization-intramolecular ester enolate alkylation

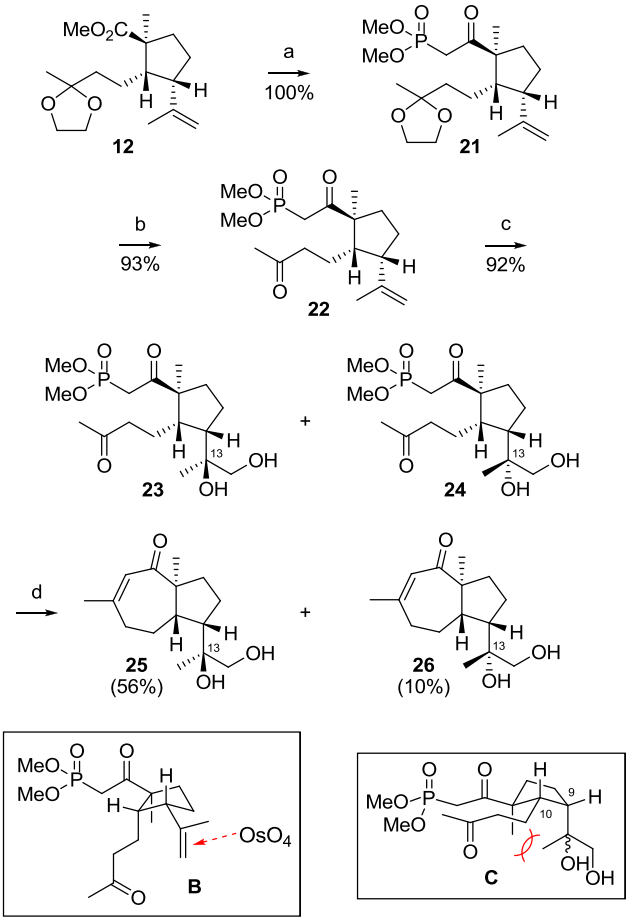
Our '*folding and allylic strain-controlled*' intramolecular ester enolate alkylation of tosylate **13** with KHMDS in THF at −60 °C to 0 °C for 1 h generated the desired cyclopentanecarboxylate **12** in 85% yield with a 30:1 stereoselectivity[18] at the newly generated C(6) quaternary carbon center. This IEEA process establishes the required relative stereochemistry of the three contiguous stereogenic centers at C(6), C(10), and C(9) of the natural product (Scheme 4). The observed high stereoselectivity of this intramolecular alkylation can best be rationalized by invoking the most stable '*H-eclipsed*' transition state geometry as depicted in **A**, which appears to be of highly congested.

2.4. Construction of the bicyclic framework via Horner–Wadsworth–Emmons olefination

Having established the desired three contiguous stereogenic centers in the cyclopentane subunit of the natural product, we next focused our attention on completing the bicyclic hydroazulene framework by means of an internal Horner–Wadsworth–Emmons olefination (Scheme 5).

Toward this end, condensation of ester **12** with excess lithium dimethylphosphonate[19] afforded β-ketophosphonate **21**, and acidic cleavage of the dioxolane group in **21** correspondingly furnished **22** in excellent yield (93% over two steps). To incorporate the side chain efficiently and preclude epimerization at C(9), we initially opted for an epoxide as the acceptor, which would be derived via a vicinal diol. For this scenario, however, the crucial dihydroxylation[20] of olefin **22** with OsO_4–NMO produced a 6:1 diastereomeric mixture (at C(13)) of **23**/**24** that favored the undesired isomer. This inopportune facial selectivity might be rationalized by invoking electrophilic attack on the *si*-face of the alkene in conformation **B**.

To corroborate this hypothesis, we performed density functional theory (DFT) calculations to quantify the conformational energetics of **22** and also to compare the energetics of competing osmylation transition structures leading to **23**/**24**. A simplified model was used to describe isoprenylcyclopentane **22**, replacing side chains by methyl groups, in an attempt to preserve their steric influence near to the ring in our model. A number of low energy conformations within 1.5 kcal/mol were located, of which the two lowest are shown (Fig. 5). They differ by the orientation of the isoprenyl group—the more stable conformer exposes the alkene *si*-face that is attacked to form the major dihydroxylation product. However, the B3LYP and M06-2X energy difference between these conformations is very small such that it does not account for the magnitude of the experimentally observed selectivity of 6:1. This led us to compute the structures of the two osmylation transition structures (Fig. 5). Now, the calculated energetic difference is in the correct sense with respect to experiment, and is 0.7 (corresponding to a 3:1 ratio of **23**/**24**) or 1.2 kcal/mol (a 7:1 ratio) with the B3LYP or M06-2X functional. The near-quantitative agreement of TS relative energies point toward a kinetic origin of selectivity. This selectivity arises from a difference in unfavorable interactions between the



Scheme 5. Reagents and conditions: (a) $(MeO)_2P(O)Me$, *n*-BuLi, THF, −78 °C, 2 h (100%); (b) PTSA (cat.), H_2O, acetone, rt, 24 h (93%); (c) OsO_4 (cat.), NMO, aqueous acetone, rt, 2 h (6:1 at C(13), 92%); (d) K_2CO_3, 18-crown-6, benzene, reflux, 20 h, (**25**/**26**=5.6:1, 66%).

three *syn*-substituents (Me, Me, isoprenyl). To form **23**, the alkenyl group must be oriented downwards in a hindered position, while in the formation of **24** the methyl group is instead oriented downwards within van der Waals contact of the two other groups on the same face. Removing the transannular steric interactions from our model, while rigidly maintaining the positions of the C, O, and Os atoms at their positions in the optimized transition structure, leads to an energetic difference of just 0.1 kcal/mol between pathways. This suggests that it is these unfavorable interactions that are the major contributor in the stereoselectivity of this osmylation step.

Although the dihydroxylation approach gave the undesired isomer as a major product, we recognized that the vicinal diol mixture could be converted to the corresponding carbonyl functionality by oxidative cleavage under conditions that would preclude epimerization. This would enable the diol group in **23** to serve as a latent ketone to be revealed at the proper time for the late-stage coupling reaction. Another advantage of this strategy is that it circumvents potential problems with α-epimerization of the ketone moiety at C(9) that may arise under the basic HWE conditions in the cyclization step.

Unlike the case of the *trans*/*anti*-β-ketophosphonate (DBU, LiCl, MeCN, rt, 24 h, 85%)[5c] that served as the penultimate intermediate for our synthesis of (−)-reiswigin A, intramolecular Horner–Wadsworth–Emmons olefination of the *trans*/*syn*-β-ketophosphonate diastereomeric mixture **23**/**24** proved to be of significant challenge, presumably due to unfavorable steric interactions between the C(6) methyl and the C(9) *tert*-carbinol moiety in the transition state depicted in **C**. We reasoned that this would retard access to the conformation that is required for ring closure. After some experimentation, we were pleased to find that subjection of a 6:1 β-ketophosphonates mixture **23**/**24** to forcing conditions (K_2CO_3, 18-crown-6, benzene, reflux, 20 h) effected the crucial internal HWE olefination to provide the desired bicyclic enone **25** (56%), along with its separable C(13)-isomer **26** (10%).[21]

2.5. Completion of the synthesis of (±)-tormesol (1)

With key bicyclic intermediates **25** and **26** in hand, we proceed to address the assembly of the side chain appendage and the removal of the oxygen function at C(5) to complete the synthesis.

To this end, the α,β-unsaturated enone mixture **25**/**26** was reduced with $NaBH_4$ to afford the corresponding allylic alcohols **27**/**28** in quantitative yield (Scheme 6). Oxidative cleavage of the 1,2-diol moiety in triol mixture **27**/**28** with $NaIO_4$ led to the desired ketone **10** in 92% yield, setting the stage for the crucial Grignard reaction. In addition, the *trans*/*syn*-ketone **10** undergoes facile epimerization to the corresponding trans/*anti*-isomer **29** in quantitative yield upon treatment with KOH in THF/MeOH/H_2O at rt. Thus, it is worthwhile to note that our strategy has the unique advantage that intermediate ketone **10** provides access to both *trans*/*syn*- and *trans*/*anti*-sphenolobane diterpenes, as exemplified by tormesol and 3α,4α-epoxy-5α,18-dihydroxysphenolobana-13*E*,16*E*-diene.

The addition of homoprenyl Grignard reagent (4-methyl-3-pentenylmagnesium bromide) to ketone **10** produced the desired *tert*-carbinol **30** in low yield (30%), along with reduced product **31** (25%) and the recovered reactant ketone **10** (30%), as was found by the Tori group. However, mindful that cerium-promoted Grignard additions are known to be highly selective with enolizable ketones, we were pleased to find that treatment of ketone **10** with homoprenyl Grignard reagent in the presence of $CeCl_3$ in THF at 0 °C according to the protocol of Imamoto[22] furnished the desired *tert*-carbinol **30** in excellent yield (92%) with a 6.7:1 selectivity at C(13) (Scheme 7).[23] The observed diastereoselectivity can be rationalized by invoking nucleophilic attack from the less hindered *si*-face of the ketone **10** depicted in conformation **D**.

Selective conversion of the allylic secondary carbinol to the methylene by a two-step process served us quite well. Diol **30** was converted to the corresponding allylic acetate **32**, and after a considerable amount of experimentation we were pleased to find that subjection of acetate **32** to dissolving metal reduction conditions (K, 18-crown-6, *t*-$BuNH_2$, THF)[24] effected deoxygenation to deliver a 60% yield of synthetic (±)-tormesol (**1**) along with its regioisomers **33** (20%) and **34** (10%). All three isomers were separable by column chromatography using $AgNO_3$-impregmented silica gel, and their structures were characterized by NMR spectroscopy. The spectral data for synthetic (±)-tormesol (**1**) were identical in every respect with those reported for the natural compound (^1H, ^{13}C, IR, and HRMS).[25]

2.6. Confirmation of the configuration of tertiary alcohol at C(13) and the synthesis of (±)-13-*epi*-tormesol 38

Although we had successfully achieved the synthesis of (±)-tormesol (**1**), we envisaged that chemical transformations of both diols **23**/**24** to the corresponding final compounds (i.e., tormesol and C(13)-*epi*-tormesol) would leave no doubt as to the identity of the diastereomers obtained from dihydroxylation (vide supra). In the event, both triols **27** (major) and **28** (minor) obtained from $NaBH_4$ reduction were separately converted to the corresponding epoxide **35** and **39**, respectively, via selective tosylation of the primary hydroxyl group and subsequent internal Williamson ether synthesis (Scheme 8). Opening of epoxide **35** with prenyl Grignard reagent (3-methyl-2-butenylmagnesium chloride) in the

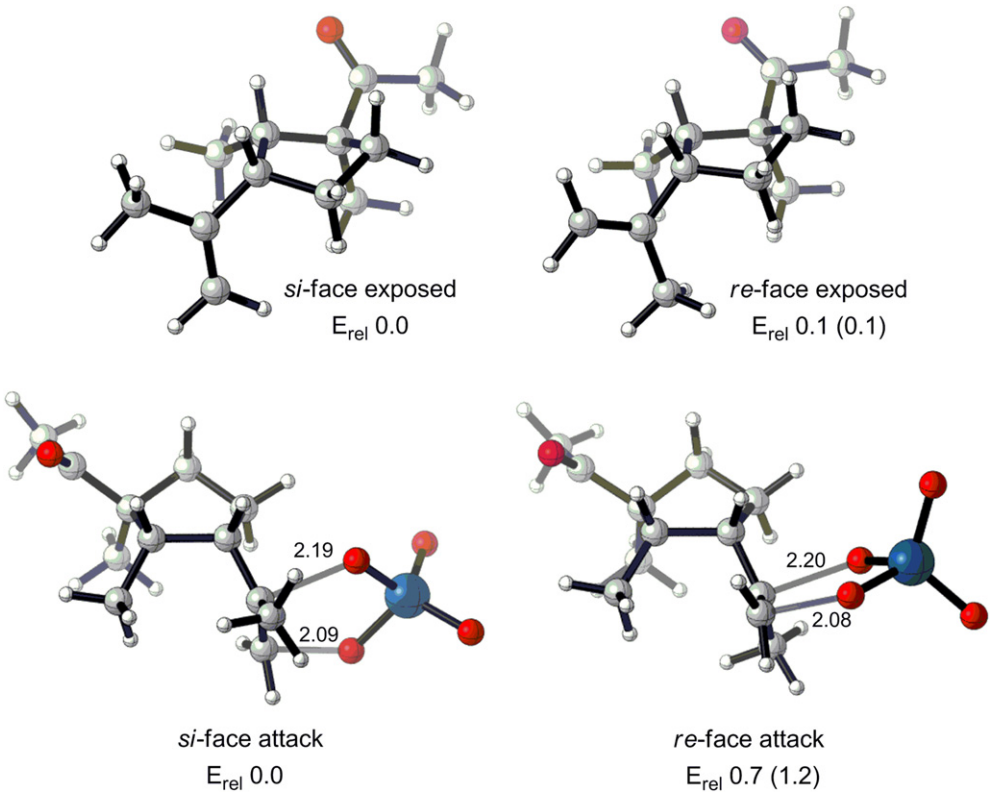
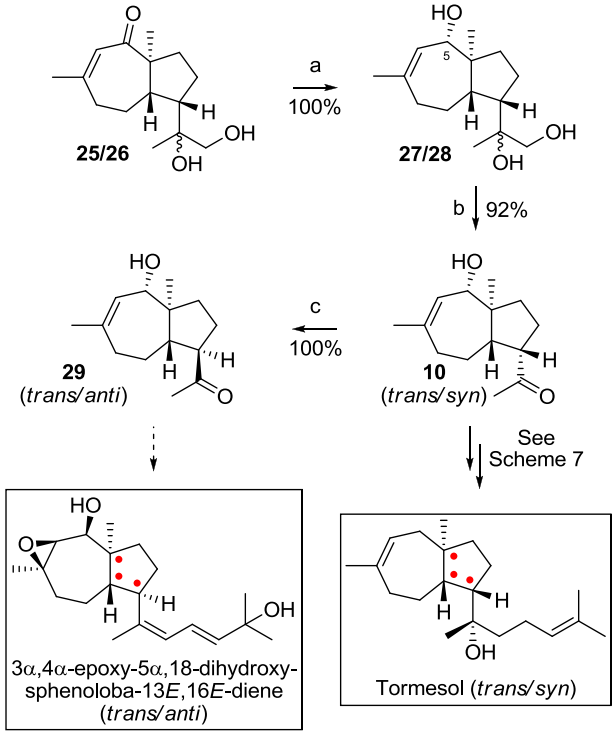


Fig. 5. Optimized geometries of lowest energy conformations for models of **22** and osmylation TS to **23** and **24**. B3LYP energetics, M06-2X in parentheses, in kcal/mol. Selected distances in Å.

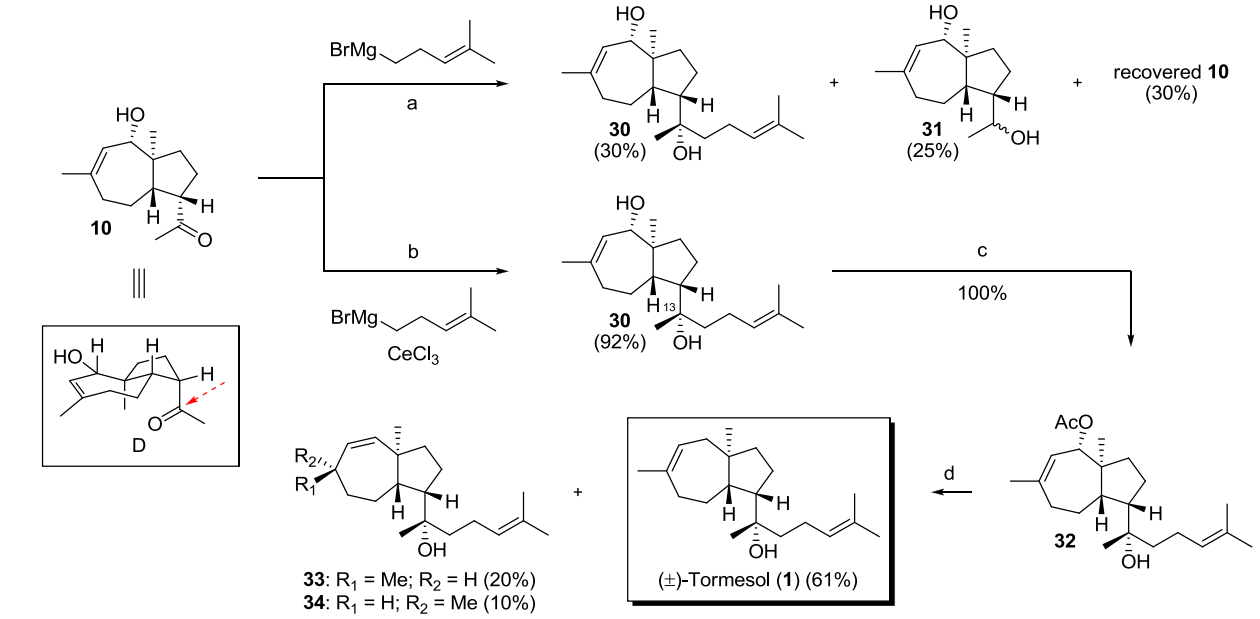


Scheme 6. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 1.5 h (100%); (b) $NaIO_4$, acetone/H_2O (2:1), 0 °C, 0.5 h (92%); (c) KOH, THF/MeOH/H_2O (3:1:1), rt, overnight (100%).

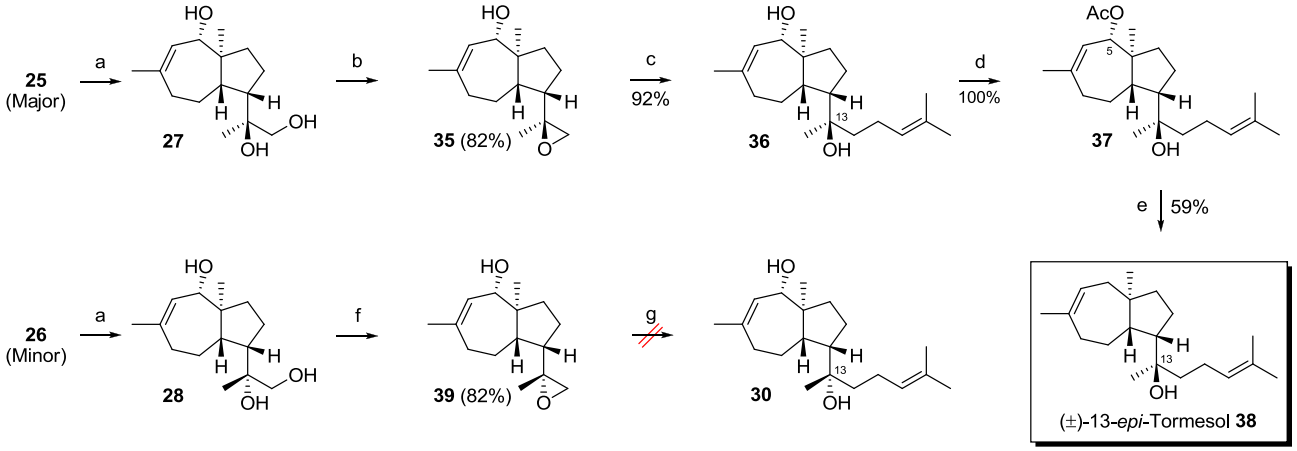
presence of CuI according to the protocol of Johnston[26] then efficiently gave rise to epimeric tertiary alcohol **36** in excellent yield (92%). Interestingly, opening of the epoxide **39** that was derived from minor diol **24** in the dihydroxylation did not lead to **40** under similar conditions. Finally, dissolving metal reduction of the secondary hydroxyl at C(5) in **36** via acetate **37** under conditions identical to those used for the synthesis of (±)-tormesol (**1**) afforded (±)-13-*epi*-tormesol **38** in 60% yield and its regiomeric isomers in 30% yield. The obvious differences between **38** and **1** (^1H and ^{13}C NMR) together with the safe assumption that and epimerization at C(9) is not possible during the epoxide-opening sequence prompted us to confirm that **38** should be a C(13) epimer of **1**. We were then able quickly to determine the stereochemical outcome at the dihydroxylation stage.

3. Conclusion

We have completed a highly stereocontrolled total synthesis of (±)-tormesol (**1**) in 18 steps and 4.1% overall yield from known aldehyde **16** in a substrate-controlled fashion with minimal use of protecting groups. The most rewarding aspects of this synthesis were: (1) the stereoselective construction of this challenging trisubstituted cyclopentane framework with a trans/*syn*-configuration, based upon intramolecular ester enolate alkylation (IEEA) as a key strategy, (2) a demanding internal Horner–Wadsworth–Emmons olefination for the construction of the hydroazulene skeleton, and (3) an efficient and stereoselective Grignard reaction for the control of the stereochemistry at C(13) of the side chain appendage without epimerization at C(9). It is also significant that our methodology provides optional access to the stereoisomers at C(13) in the flexible side chain in the trans/*syn* bicyclic system through the judicious choice between an epoxide opening and



Scheme 7. Reagents and conditions: (a) homoprenylmagnesium bromide, Et_2O, 0 °C, 0.5 h, **30** (30%), **31** (25%), **10** (30%); (b) homoprenylmagnesium bromide, $CeCl_3$, THF, 0 °C, 0.5 h (6.7:1 at C(13), 92%); (c) Ac_2O, DMAP, pyridine, CH_2Cl_2, 0 °C, 0.5 h (100%); (d) K, 18-crown-6, *t*-$BuNH_2$/THF (4:1), rt, 10 min, (±)-tormesol (**1**) (61%), **33** (20%), **34** (10%).



Scheme 8. Reagents and conditions: (a) $NaBH_4$, MeOH, 0 °C, 1 h, **27** (100%), **28** (100%); (b) TsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 0.5 h, then K_2CO_3, MeOH, rt, **35** (82%), **39** (82%); (c) prenylmagnesium chloride, CuI, THF, −20 °C to rt (92%); (d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C, 0.5 h (100%); (e) K (metal), 18-crown-6, *t*-$BuNH_2$/THF (4:1), rt, 10 min, (±)-13-*epi*-tormesol **38** (59%); (f) prenylmagnesium chloride, CuI, THF, 0 °C.

ketone addition using a common diol intermediate obtained via diastereoselective osmylation. Currently, efforts are being made to broaden this internal S_N2 alkylation tactic, and adapt it in our laboratories to the syntheses of other synthetically challenging natural products that possesses the trans/*anti*-configuration.

4. Experimental section

4.1. Preparation of *trans*-lactone 14

To a cooled (0 °C) solution of CuI (1.05 g, 5.54 mmol) in THF/Et_2O (1:1, total 40 mL) was added dropwise isopropenylmagnesium bromide (19.1 mL, 0.5 M in THF, 9.6 mmol). The resulting dark suspension was stirred at the same temperature for 30 min. The solution of butenolide **15** (1.00 g, 5.04 mmol) in THF (4 mL) was added dropwise at −50 °C for 10 min. After being stirred for 5 min at the same temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl/NH_4OH (4:1, total 100 mL), diluted with diethyl ether (200 mL), and stirred for overnight. The layers were separated, and the aqueous layer was extracted with diethyl ether (1×50 mL). The combined organic layer were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 3:1) to give *trans*-γ-lactone **14** as a colorless oil (920.0 mg, 76%): ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (s, 1H), 4.88 (s, 1H), 4.32–4.36 (m, 1H), 3.90–3.98 (m, 4H), 2.81 (ddd, J=8.7, 8.7, 8.4 Hz, 1H), 2.67 (dd, J=17.5, 8.7 Hz, 1H), 2.51 (dd, J=17.5, 9.6 Hz, 1H), 1.64–1.92 (m, 4H), 1.76 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 141.7, 113.7, 109.4, 83.4, 64.64, 64.61, 48.7, 34.8, 34.1, 29.0, 23.8, 19.5; IR (neat) 2919, 1771 cm^{-1}; HRMS (EI) found 240.1347 [calcd for $C_{13}H_{20}O_4$ $(M)^+$ 240.1362].

To a cooled (−60 °C) solution of tosylate **13** (792.4 mg, 1.69 mmol) in anhydrous THF (170 mL, 0.01 M) was added dropwise a solution of KHMDS (3.4 mL, 1.0 M in THF, 3.4 mmol). After being stirred at the same temperature for 20 min, the reaction mixture was rapidly allowed to warm to 0 °C and stirred for 40 min. The

reaction mixture was quenched with saturated aqueous NH_4Cl, and diluted with diethyl ether (300 mL). The layers were separated, and the aqueous layer was extracted with diethyl ether (2×100 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 30:1) to give the *trans*-cyclopentanecarboxylate **12** as a colorless oil (386.1 mg, 85%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (s, 1H), 4.70 (s, 1H), 3.86–3.95 (m, 4H), 2.51 (ddd, *J*=8.4, 8.4, 8.4 Hz, 1H), 2.31–2.37 (m, 2H), 1.73 (s, 3H), 1.53–1.73 (m, 5H), 1.29 (s, 3H), 1.25 (s, 3H), 1.22–1.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.4, 145.8, 111.4, 110.0, 64.57, 64.52, 53.6, 52.0, 50.1, 47.6, 39.1, 34.5, 26.2, 23.55, 23.46, 20.9, 19.9; IR (neat) 2952, 1728 cm^{-1}; HRMS (EI) found 296.1988 [calcd for $C_{17}H_{28}O_4$ (M)$^+$ 296.1988].

4.2. Preparation of azulenes 25/26

To a solution of diol **23**/**24** (70.4 mg, 0.204 mmol) in anhydrous benzene (35 mL, 0.006 M) were added K_2CO_3 (84.6 mg, 0.612 mmol) and 18-crown-6 (323.5 mg, 1.22 mmol). After being stirred at 80 °C for 24 h, the reaction mixture was diluted with diethyl ether/H_2O (5:1, total 60 mL). The layers were separated, and aqueous layer was extracted with diethyl ether (2×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, *n*-hexanes/ethyl acetate, 3:1) to give azulene **25** (27.6 mg, 56%) along with olefin positional isomer **26** (5.1 mg, ~10%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (s, 1H), 3.44 (d, *J*=10.7 Hz, 1H), 3.31 (d, *J*=10.7 Hz, 1H), 2.64–2.69 (m, 1H), 2.29–2.53 (m, 6H), 2.00–2.03 (m, 1H), 1.89 (s, 3H), 1.67–1.79 (m, 3H), 1.25–1.35 (m, 1H), 1.22 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.7, 152.8, 126.8, 75.4, 70.4, 56.2, 46.8, 44.1, 35.85, 35.72, 28.4, 26.1, 22.7, 20.8, 20.4; IR (neat) 3463, 2965, 1659 cm^{-1}.

4.3. Preparation of tertiary alcohol 30

To a cooled (0 °C) suspension of ketone **10** (29.7 mg, 0.16 mmol) and $CeCl_3$ (78.9 mg, 1.28 mmol) in THF (5.0 mL, 0.032 M) was added homoprenylmagnesium bromide (6.5 mL, 0.37 M in Et_2O, 2.40 mmol). After being stirred at the same temperature for 30 min, the reaction mixture was quenched with saturated aqueous NH_4Cl, acidified with acetic acid (~0.5 mL), and diluted with diethyl ether (20 mL). The layers were separated, and aqueous layer was extracted with diethyl ether (2×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 10:1) to give tertiary alcohol **30** (32.9 mg, 80%) along with its 13-epimer (5.1 mg, 12%) as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (s, 1H), 5.12 (dd, *J*=7.0, 7.0 Hz, 1H), 3.94 (s, 1H), 2.45 (ddd, *J*=10.3, 10.3, 10.0 Hz, 1H), 1.95–2.20 (m, 4H), 1.90 (dd, *J*=12.9, 12.9 Hz, 1H), 1.85 (ddd, *J*=12.2, 12.2, 1.4 Hz, 1H), 1.62–1.75(m, 2H), 1.75 (s, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 1.44–1.56 (m, 4H), 1.21–1.33 (m, 1H), 1.19 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 131.8, 130.1, 124.7, 80.7, 75.8, 53.5, 52.6, 47.6, 39.7, 37.9, 35.8, 28.0, 26.8, 25.9, 25.7, 23.4, 22.8, 17.7, 13.9; IR (neat) 3445, 2922, 1454, 1375, 1265, 1017 cm^{-1}; HRMS (EI) found 270.2348 [calcd for $C_{20}H_{30}$(M−2H_2O)$^+$ 270.2348].

4.4. Preparation of (±)-tormesol (1)

Small freshly cut pieces of oil-free potassium (135 mg-atom) were added to a solution of 18-crown-6 (211.2 mg, 0.8 mmol) in anhydrous *tert*-butylamine (8 mL) at room temperature. The mixture was stirred at the same temperature until a dark-blue color developed, and then anhydrous THF (2 mL) was added. A solution of acetate **32** (35.2 mg, 0.100 mmol) in anhydrous THF (4 mL) was immediately added upon appearance of the blue color at such a rate that the color did not disappear for long periods. After addition of all the substrate and reappearance of the blue color (~30 min), the excess potassium was destroyed with absolute ethanol. The resulting mixture was neutralized saturated aqueous NH_4Cl, and diluted with Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 50:1) to afford (±)-tormesol (**1**) along with its $\Delta^{4,5}$-isomers (total 27.2 mg, 93%, $\Delta^{3,4}$:$\Delta^{4,5}$=2:1, ^{1}H NMR analysis). This mixture was purified rigorously by chromatography ($AgNO_3$-impregnated silica gel, hexanes/ethyl acetate, 100:0 to 100:1) to afford (±)-tormesol (**1**) as a colorless oil (17.8 mg, 61%). The spectral characteristics the synthetic (±)-tormesol (**1**) were in agreement with those of the natural product.

4.5. Preparation of 13-*epi*-tertiary alcohol 36

To a cooled (0 °C) suspension of epoxide **35** (6.0 mg, 0.025 mmol) and CuI (14.5 mg, 0.076 mmol) in THF (1 mL, 0.025 M) was added prenylmagnesium chloride (0.4 mL, 1.94 M in THF, 0.78 mmol), which was generated in situ by the addition of prenyl chloride (0.33 mL, 2.93 mmol) into the suspension of magnesium turnings in THF (1.51 mL) at 0 °C. After being stirred at the same temperature for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl, and then extracted with ethyl acetate (2×10 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 8:1) to give tertiary alcohol **36** (7.15 mg, 92%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.24 (s, 1H), 5.12 (dd, *J*=7.0, 7.0 Hz, 1H), 3.94 (s, 1H), 2.45 (ddd, *J*=10.3, 10.3, 10.0 Hz, 1H), 1.95–2.20 (m, 4H), 1.90 (dd, *J*=12.9, 12.9 Hz, 1H), 1.85 (ddd, *J*=12.2, 12.2, 1.4 Hz, 1H), 1.62–1.75 (m, 2H), 1.75 (s, 3H), 1.69 (s, 3H), 1.63 (s, 3H), 1.44–1.56 (m, 4H), 1.21–1.33 (m, 1H), 1.19 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 131.8, 130.1, 124.7, 80.7, 75.8, 53.5, 52.6, 47.6, 39.7, 37.9, 35.8, 28.0, 26.8, 25.9, 25.7, 23.4, 22.8, 17.7, 13.9; IR (neat) 3445, 2922, 1454, 1375, 1265, 1017 cm^{-1}; HRMS (EI) found 270.2348 [calcd for $C_{20}H_{30}$ (M−2H_2O)$^+$ 270.2348].

4.6. Preparation of (±)-13-*epi*-tormesol 38

Small freshly cut pieces of oil-free potassium (70 mg-atom) were added to a solution of 18-crown-6 (120.0 mg, 0.45 mmol) in anhydrous *tert*-butylamine (4 mL) at room temperature. The mixture was stirred at the same temperature until a dark-blue color developed, and then anhydrous THF (1 mL) was added. A solution of acetate **37** (14.2 mg, 0.041 mmol) in anhydrous THF (2 mL) was immediately added upon appearance of the blue color at such a rate that the color did not disappear for long periods. After addition of all the substrate and reappearance of the blue color (~30 min), the excess potassium was destroyed with absolute ethanol. The resulting mixture was neutralized saturated aqueous NH_4Cl, and diluted with Et_2O (20 mL). The layers were separated and the aqueous layer was extracted with Et_2O (10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexanes/ethyl acetate, 50:1) to afford (±)-13-*epi*-tormesol **38** along with its $\Delta^{4,5}$-isomers (total 10.8 mg, 91%, $\Delta^{3,4}$:$\Delta^{4,5}$=2:1, ^{1}H NMR analysis). This mixture was purified rigorously by chromatography ($AgNO_3$-impregnated silica gel, *n*-

hexane/ethyl acetate, 100:0 to 100:1) to afford (±)-13-*epi*-tormesol **38** as a colorless oil (6.9 mg, 59%).

4.7. DFT calculations

All geometries were optimized at the B3LYP/6-31G(d) level of theory, after which single point energy calculations were performed at the B3LYP/6-311+G(d,p) and M06-2X/6-311+G(d,p) levels. Osmylation transition structures employ a LANL2DZ ECP and associated valence basis for Os. Stationary points were verified as minima and transition structures by the presence of zero and one imaginary vibrational frequency, respectively.

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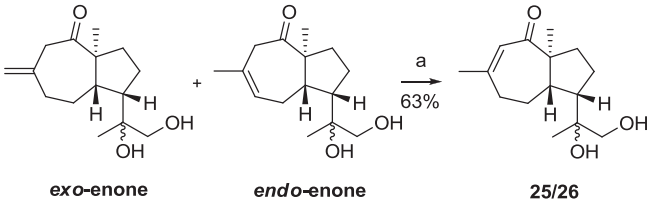
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.022.

References and notes

1. Major portions of this work were taken from Lee, D. M.S. Dissertation, Seoul National University, 2000. After the completion of our work, a synthesis of the antipode of tormesol was published by the Tori group.
2. (a) From *Pseudolarix kaempferi* Gordon: Zhou, B. N.; Ying, B. P.; Song, G. Q.; Chen, Z. X.; Han, J.; Yan, Y. F. *Planta Med.* **1983**, *47*, 35; From *Anastrophyllum minutum*: Beyer, J.; Becker, H.; Toyata, M.; Asakawa, Y. *Phytochemistry* **1987**, *26*, 1085; (b) From *Anastrophyllum auritum*: Zapp, J.; Burkhardt, G.; Becker, H. *Phytochemistry* **1994**, *37*, 787; (c) From *Anastrophyllum donnianum*: Buchanan, M. S.; Connolly, J. D.; Rycroft, D. S. *Phytochemistry* **1996**, *43*, 1297.
3. (a) From *Epipolasis reiwigi* (Reiswigin A and B): Kashman, Y.; Hirsch, S.; Koehn, F.; Cross, S. *Tetrahedron Lett.* **1987**, *28*, 5461; (b) From *Epipolasis* sp. (Polasols A–C): Umeyama, A.; Nozaki, M.; Arihara, S. *J. Nat. Prod.* **1998**, *61*, 945.
4. The numbering system of sphenolobane follows that proposed by Connolly: Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapmann & Hall: London, UK, 1991.
5. Reiswigin A: (a) Snider, B. B.; Yang, K. *Tetrahedron Lett.* **1989**, *30*, 2465; (b) Snider, B. B.; Yang, K. *J. Org. Chem.* **1990**, *55*, 4392; (c) Kim, D.; Shin, K. J.; Kim, I. Y.; Park, S. W. *Tetrahedron Lett.* **1996**, *35*, 7957.
6. Pseudolaric Acids: (a) Geng, Z.; Chen, B.; Chiu, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 6197; (b) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2007**, *129*, 14556; (c) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424; (d) Xu, T.; Li, C.-C.; Yang, Z. *Org. Lett.* **2011**, *13*, 2630.
7. Tormesol: (a) Nakashima, K.; Inoue, K.; Sono, M.; Tori, M. *J. Org. Chem.* **2002**, *67*, 6034; (b) Nakashima, K.; Fujisaki, N.; Inoue, K.; Minami, A.; Nagaya, C.; Sono, M.; Tori, M. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1955.
8. Urones, J. G.; Marcos, I. S.; Garrido, N. M.; de Pascual Teresa, J.; Martin, A. S. F. *Phytochemistry* **1989**, *28*, 183.
9. (a) Marcos, I. S.; Oliva, I. M.; Díez, D.; Moro, R. F.; Díez, D.; Urones, J. G. *Tetrahedron* **1994**, *50*, 12655; (b) Marcos, I. S.; Oliva, I. M.; Díez, D.; Basabe, P.; Lithgow, A. M.; Moro, R. F.; Garrido, N. M.; Urones, J. G. *Tetrahedron* **1995**, *51*, 12403.
10. Djerrasi, C. *Dictionary of Natural Products*; Chapmann & Hall: Cambridge, UK, 1994.
11. (a) Stork, G.; Uyeo, S.; Wakamatsu, T.; Grieco, P.; Labovitz, J. *J. Am. Chem. Soc.* **1971**, *93*, 4945; (b) Stork, G.; Zhao, K. *J. Am. Chem. Soc.* **1990**, *93*, 5875.
12. Ahn, S. H.; Kim, D.; Chun, M. W.; Chung, W. *Tetrahedron Lett.* **1986**, *27*, 943.
13. (a) **Cyclobutanecarboxylate**: Kim, D.; Jang, Y. M.; Kim, I. O.; Park, S. W. *Chem. Commun.* **1988**, 760; (b) Kim, D.; Lee, Y. K.; Jang, Y. M.; Kim, I. O.; Park, S. W. *J. Chem. Soc., Perkin Trans. 1* **1990**, 3221; (c) Kim, D.; Kwak, Y. S.; Shin, K. J. *Tetrahedron Lett.* **1994**, *35*, 9211; (d) **Cyclopentanecarboxylate**: Kim, D.; Shin, K. J.; Kim, I. Y.; Park, S. W. *Tetrahedron Lett.* **1994**, *35*, 7957; (e) Kim, D.; Lim, J. I. *Tetrahedron Lett.* **1995**, *36*, 5035; (f) Kim, D.; Kim, I. H. *Tetrahedron Lett.* **1997**, *38*, 415; (g) Kim, D.; Lee, J.; Shim, P. J.; Jo, H.; Kim, S. *J. Org. Chem.* **2002**, *67*, 764; (h) Kim, D.; Lee, J.; Shim, P. J.; Lim, J. I.; Doi, T.; Kim, S. *J. Org. Chem.* **2002**, *67*, 772; (i) Lee, J.; Hong, J. *J. Org. Chem.* **2004**, *69*, 6433; (j) **Cyclohexanecarboxylate**: Kim, D.; Kim, H. *J. Org. Chem.* **1987**, *52*, 4633; (k) Kim, D.; Kim, S.; Lee, J. J.; Kim, H. S. *Tetrahedron Lett.* **1990**, *31*, 4027; (l) Kim, D.; Kim, H. S.; Yoo, J. Y. *Tetrahedron Lett.* **1991**, *32*, 1577; (m) Kim, D.; Lim, J. I.; Shin, K. J.; Kim, H. S. *Tetrahedron Lett.* **1993**, *34*, 6557; (n) Kim, D.; Choi, W. J.; Hong, J. Y.; Park, I. Y.; Kim, Y. B. *Tetrahedron Lett.* **1996**, *37*, 1433; (o) Kim, D.; Ahn, S. K.; Bae, H.; Choi, W. J.; Kim, H. S. *Tetrahedron Lett.* **1997**, *38*, 4437; (p) Kim, D.; Lee, J.; Chang, J.; Kim, S. *Tetrahedron* **2001**, *57*, 1247.
14. For a review of cyclopentanoids natrural product with IEEA: Kim, D. *Korean J. Med. Chem.* **1996**, *6*, 285.
15. Taylor, W. G. *J. Org. Chem.* **1979**, *44*, 1020.
16. Overman, L. E.; Thompson, A. S. *J. Am. Chem. Soc.* **1988**, *110*, 2248.
17. Youn, I. K.; Yon, G. H.; Pak, C. S. *Tetrahedron Lett.* **1986**, *27*, 2409.
18. Both major and minor diastereomers at C(6) were readily able to be separated by silica gel column chromatography.
19. Corey, E. J.; Kwiatkowski, G. T. *J. Am. Chem. Soc.* **1966**, *88*, 5654.
20. VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *25*, 1973.
21. A small quantity of a mixture of *exo*- and *endo*-β,γ-unsaturated enones was obtained in the course of Intramolecular Horner–Wadsworth–Emmons olefination. Both of these enones could be converted to the desired α,β-unsaturated enones in 63% yield by treatment of them with DBU in CH_2Cl_2 for 20 h at rt.



22. Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.
23. It is interesting to note that a related *trans*/*syn*-ketone produced a roughly 1:1 mixture of the corresponding tertiary alcohols upon exposure to 4-methyl-3-pentenyllithium (homoprenyllithium); Ref. 9b.
24. Barrett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501.
25. ^{1}H and ^{13}C NMR spectra for natural sample were provided by Dr. Urones; We are grateful to Dr. Urones for copies of NMR spectra of (+)-tormesol.
26. (a) Johnston, B. D.; Slessor, K. N. *Can. J. Chem.* **1978**, *57*, 233; (b) Johnston, B. D.; Oelschlager, A. C. *J. Org. Chem.* **1986**, *51*, 760.